UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO WAVE 1 CASES**	**Master File No. 2:12-MD-02327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

RULE 26 EXPERT REPORT OF DR. DANIEL ELLIOTT

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I. Background and Qualifications

I am an Associate Professor of Urology at Mayo Graduate School of Medicine in Rochester, Minnesota. I received an M.D. in 1993 from Loma Linda University School of Medicine in Loma Linda, California. Following graduation from medical school, I completed my surgical residency in Urology at the Mayo Graduate School of Medicine at the Mayo Clinic in 1999. I then completed a one-year advanced surgical fellowship at Baylor College of Medicine in Houston, Texas, in Neurourology, Urodynamics and Voiding Dysfunction. I then re-joined the faculty at the Mayo Clinic, where I have spent the last 15 years specializing in treating pelvic organ prolapse and urinary incontinence in women and urinary incontinence in men. I have published over 60 peer-reviewed articles and given over a hundred lectures, many of which relate to urinary incontinence and pelvic organ prolapse. A Mayo Clinic colleague and I were the first to perform robotic sacrocolpopexy surgery for the treatment of high-grade prolapse and to publish extensively on the subject. I am a frequent invited lecturer at medical and surgical conferences addressing pelvic organ prolapse and stress urinary incontinence and their evaluation, treatments, surgical options and management of complications. I have taken and passed the subspecialty credentialing process recently established by the combined boards of the American Board of Urology and American Board of Obstetrics and Gynecology in Female Pelvic Medicine and Reconstructive Surgery.

Attached, as Exhibit "A", to this report is a copy of my current curriculum vitae, which includes an up-to-date list of my publications, presentations, awards, and other academic activities.

II. Basis of Opinion

I have been asked to provide opinions regarding the subject of female stress urinary incontinence, its evaluation, treatments, surgical options and management of complications as well as to address the actions of Ethicon, Inc., Ethicon Women's Health and Urology, a Division of Ethicon, Inc., Gynecare and Johnson & Johnson (collectively referred to as Ethicon). The focus of my investigation for this report is on the Tension-Free Vaginal Tape-Retropubic ("TVT") and, specifically, the characteristics of the product that make it defective or, in other words, that make the risks to the patient outweigh the benefits to the patients. My opinions are based on my personal knowledge, experience, and my investigation in this case. All of my opinions, and the basis of those opinions, are true and correct to the best of my knowledge and belief, including those related to scientific and medical issues, which I believe are true and correct to a reasonable degree of scientific and medical certainty. I do, however, reserve the right to supplement this report and my opinions in light of any additional material or information provided to me, including any reports submitted and/or any other discovery that is taken in this case. Furthermore, if called to testify, I would plan to use various demonstrative exhibits, animations, video recordings, and/or anatomic models to show the relevant anatomy and surgical procedures and to describe my opinions as set forth in this report.

My opinions and conclusions regarding the Tension-Free Vaginal Tape product, its surgical procedure, its impact on patients and surgical colleagues, as covered throughout this report, have not been derived in isolation or are the basis of solitary data and opinion; rather, my report has been formed and influenced by multiple sources, briefly summarized as follows. My independent clinical and laboratory mesh-specific research including clinical manuscripts pertaining to female SUI, female pelvic organ prolapse, including mesh-specific complications;

animal laboratory studies regarding the effects of polypropylene mesh and host foreign body response and inflammatory response; by advanced surgical fellowship training in Voiding Dysfunction and Neurourology, which is above and beyond the normal six-year urologic surgical training and my personal surgical, clinical, and research experience implanting synthetic mesh slings; my personal surgical, clinical, and research experience as a Female Pelvic Medicine and Reconstructive surgical specialist at a high volume tertiary center managing highly complicated SUI patients and the management of mesh-related complications, including the medical and surgical revisions, removal and treatment of synthetic mesh slings complications, including complications caused by the Ethicon TVT device; my attendance and participation at national and international Urological and Gynecological surgical meetings, including, but not limited to the International Pelvic Pain Society, International Continence Society meeting, Society of Female Urology and Urodynamics meeting, American Urologic Association meeting, Canadian Urological Association meeting, UCLA State of the Art Urology meeting, European Urological Association Subsection of Female Urology and Reconstructive Urology have also helped to form my opinions. I have prepared and have given lectures specifically focused on the complexities of treating female SUI and the management of complications associated with such treatments at national and international lectures including, but not limited to the International Continence Society meeting, Society of Female Urology and Urodynamics meeting, American Urologic Association meeting, Canadian Urological Association meeting, UCLA State of the Art Urology meeting, European Urological Association Subsection of Female Urology and Reconstructive Urology. I have had personal interactions and discussion with national and international urologic, gynecologic, urogynecologic and general surgery colleagues regarding the management of SUI in women, manifestation of mesh-specific complications and the treatment of mesh-

specific complications. As part of my interest in being as educated and as up-to-date and accurate as possible, I have reviewed the readily available medical literature pertaining to the treatment of SUI and the management of its complications from sources including but not limited to medical journals and the United States National Library of Medicine and the National Institute of Health.

I am a surgical journal editor and/or reviewer for 15 urologic and/or gynecologic journals (please see Curriculum Vitae for complete listing of journals) and was named Best Reviewer in Female Urology/Incontinence/Neurourology for two consecutive years (2012-2013) for the Journal of Urology. This is the highest honor awarded by the Editor of the Journal of Urology for excellence in manuscript review and preparation.

I have also performed a systematic review of internal Ethicon documents as they pertain to surgical mesh, TVT, the TVT procedure, expected SUI surgical results, expected SUI complications and rates of SUI complications, and marketing strategies designed for my surgical colleagues in urology, gynecology and urogynecology as well as for potential SUI patients. I have also reviewed the testimony of Ethicon employees. The materials I have reviewed and relied upon to form my opinion for this report are contained throughout the report and attached as Exhibit "B".

III. Summary of Opinions

A. Background on SUI and Treatments

B. History of Synthetic Mesh Use in Surgery

C. The Polypropylene Mesh in the TVT Should Not Be Used in the Pelvic Floor

1. Polypropylene mesh in the TVT is not inert and degrades
2. The TVT mesh is Heavyweight and Small Pore causing increased tissue response, chronic inflammatory response, contraction of the mesh, fibrotic bridging, folding and curling of the mesh, and scar plate formation
3. Ethicon's cutting process made the mesh even more dangerous

4. The TVT mesh tested positive for cytoxicity which can cause cell death and complications to women and, therefore, it should not be used in the pelvic floor

5. The TVT design is flawed because it is too difficult to properly tension the TVT device due to lack of uniformity, and the device shrinks, ropes, curls and deforms making it impossible to tension

D. Ethicon Failed to Disclose and/or Downplayed Adverse Risks, Complications and Product Information in its Instructions for Use ("IFU")

E. Ethicon Failed to Test or Conduct Appropriate Studies Related to the TVT

F. Ethicon Failed to consider numerous known risks and hazards of the TVT while designing the product.

IV. Expert Opinions

A. Background on SUI and Treatments

1. Normal Anatomy vs. Stress Urinary Incontinence

Female stress urinary incontinence ("SUI"), also known as intrinsic sphincter deficiency (ISD), is a relatively common condition in which a woman leaks urine when her body experiences an increase in abdominal pressure, which in turn increases the pressure on the bladder. The abdominal pressure (A.K.A. "stress") is caused by a wide variety of activities including coughing, laughing, sneezing, jumping, bending over, picking something up, running, or any other sudden movement that increases pressure on the bladder.

In a woman, the urine leakage caused by SUI is due to factors like to weakening of the muscles that surround the urethra and/or a lack of fascial support for the urethra. The fascia below the urethra serves as a backboard to prevent the urethra from "falling down and funneling open." SUI is much more common in women than in men, largely because of pregnancy, childbirth, menopause and hysterectomies, to mention a few. Each of these conditions cause physical changes in the fascia used to support the urethra, which in turn results or contributes to SUI. There are multiple fascias, or tissues, that support the urethra, including fascia located in

the area of the pelvic floor and endopelvic fascia. In a woman with SUI, these fascia fail to provide sufficient support for the urethra, allowing the urethra to move downward when there is a sudden increase in pressure, such as that caused by a cough or a sneeze. When this happens, urine leaks out of the urethra.

SUI can have very serious effects on a woman's physical and mental health. It is not uncommon for women with SUI to stop participating in activities they once enjoyed, such as sports and other recreational activities or experience mental illness such as depression.

2. Alternative/Traditional SUI Treatment Options

Stress urinary incontinence affects approximately 15% to 35% of women in population-based studies [Abrams et al]. While surgical treatments are generally safe and highly effective, women with stress incontinence symptoms may wish to avoid or defer surgery for medical or personal reasons. Further, expert consensus groups recommend that non-surgical options should be offered as first-line therapy for incontinence [Hays et al].

3. Behavior Modification, Pelvic Floor Therapy and Exercises

Simple lifestyle or behavioral modifications such as weight loss and/or avoidance of dietary irritants such as caffeine and nicotine are often the first line of treatment and therapy and may be the only treatment necessary. Also, pelvic floor muscle exercises (Kegel exercises) are used to strengthen the muscles surrounding the urethra so that urine is less likely to leak. These therapies require time, effort and commitment, but they do not have side effects and are often very effective.

Alternatively, pelvic floor electrical stimulation utilizes electrical current to strengthen the pelvic floor and to improve its function. Biofeedback is a treatment regimen performed under the care of a specialist and/or physical therapist. It is a safe and effective method of increasing pelvic floor strength and has a role in helping women with mild stress incontinence.

Biofeedback attempts to retrain patients on how to more appropriately use their pelvic floor muscles thereby improving their urine control. Consequently, the patient becomes more aware of her pelvic muscles and will be better able to identify and use them. Pelvic floor electrical stimulation combined with biofeedback may prove useful in that the electrical stimulation provides a passive contraction with increased awareness, via biofeedback, of pelvic muscle contractions.

4. Medication

There are several medications that have been studied for the potential treatment for SUI (Topical Estrogen, α-Adrenergic Agonists, Imipramine, Duloxetine, β-Adrenergic Antagonists, and β-Adrenergic Agonists). However, to date their benefit is minimal for SUI and is essentially limited to possibly benefiting overactive bladder.

5. Pessaries

Pessaries have been used for thousands of years to treat pelvic organ prolapse and SUI and, prior to the advent of successful surgical options; pessaries were essentially the only viable treatment for POP and SUI. Specifically, "continence pessaries" represent an alternative or complementary non-surgical approach to the treatment of stress incontinence. These devices work by providing a platform against which the urethra can compress during strenuous activity such as lifting or coughing. There are several studies describing the effectiveness of pessaries for treatment of stress incontinence but most of these studies are based on small samples of participants with short-term follow-up, which make their results questionable. Ultimately, however, due to inherent limitations of effectiveness and complications such as vaginal pain, discharge, odor and necessity of routine medical care, most patients with SUI using pessaries discontinue using the pessary.

6. Surgery

Surgeons have spent hundreds of years trying to develop successful treatments for SUI. Over the course of time, several successful surgical techniques have been devised, but all of the treatments have the common component of reestablishing support for the urethra that has been weakened and damaged by childbirth, hysterectomy, obesity and age.

7. Marshall-Marchetti-Krantz and Burch Colposuspension

In the 1940s, the Marshall-Marchetti-Krantz (MMK) procedure was developed. The MMK procedure is a surgery in which the surgeon secures the neck of the bladder—i.e., where the bladder meets the urethra—to the pubic bone with a series of sutures. The Burch colposuspension procedure is another procedure that was developed shortly after the MMK procedure. The Burch procedure is successful in treating urinary incontinence with success rates equivalent to mid-uretheral synthetic slings. The Burch procedure takes longer than a procedure to implant a synthetic mid-uretheral sling, however, the long-term complications with Burch related to chronic pain and dyspareunia are minimal when compare to mid-uretheral synthetic slings.

8. Pubovaginal Slings (Autologous/Cadaveric)

In the 1980s, a major advancement occurred with the introduction of a procedure known as the pubovaginal sling (PVS). The procedure uses harvested tissue from the tough abdominal wall tissue called abdominal fascia and then implants that tissue in the shape of a sling (hammock) around the neck of the bladder and up to the abdominal wall. Since the fascial tissue comes from the patient herself it is called "autologous" meaning tissue that comes from the same individual. The procedure rapidly rivaled the Burch colposuspension as the "gold standard" for the treatment of SUI in women. With the advent of biologic and synthetic mesh-slings the number of PVS procedures initially decreased. However, with the increasing awareness among surgeons and

patients regarding the complications (dyspareunia, life-altering pain, chronic sexual dysfunction, erosions and the others listed throughout this report) of vaginal synthetic mesh use, the PVS procedure has seen a significant resurgence. In some regions and practices around the nation, the PVS has become the mainstay of therapy. In my own personal practice, at a major tertiary referral medical center, I have abandoned essentially all synthetic mesh sling implantation due to the problems associated with complications, patients' fears, patients' refusal to have mesh inserted into their bodies and cost.[1]

B. History of Synthetic Mesh Use in General Surgery

Abdominal and thoracic wall weaknesses, called hernias, exist due to weaknesses within the abdominal wall or thoracic wall due to conditions such as birth defects, surgery, and radiation effects. Traditional hernia repair surgery evolved using sutures (stitches) to bring the native tissue together. However, due to the inherent weaknesses of the tissues, failure was common and frequently resulted in significant pain and suffering for the patient. Therefore, in the 1950s, surgical meshes for hernia repairs were introduced. Subsequently, academic presentations, surgical reports and journal manuscripts began to describe mesh-related complications such as chronic pain, abdominal wall rigidity, mesh contraction, infection, fistula formation, chronic inflammatory process and recurrence.

An abundant amount of evidence in the medical literature and basic science data has been gathered over the past two decades that indicate that there is a strong and direct relationship between postoperative mesh complications and mesh design. Reducing mesh-related complications demands a thorough understanding and knowledge of the chemical, physical and synthetic characteristics of meshes and how they react inside the human body. Based upon vast amounts of general surgery and basic science literature, there is a consensus that synthetic

meshes that are low-weight, large-pore size, high porosity, monofilament, and capable of maintaining their elasticity under load will have the better results with fewer complications. Of all the mesh characteristics, mesh stiffness, porosity and the pore size of the mesh are of critical importance.

1. Synthetic Mesh Use in Pelvic Floor

Introduced in April 1997 as a treatment for female urinary stress incontinence, the ProteGen® sling was a synthetic polymer (polyester) mesh sling implant not a polypropylene mesh as is TVT. Surgeons implanted the ProteGen polyester sling underneath the urethra to provide support and to reduce SUI. Unfortunately, nearly immediately following Protogen's launch, a large number of patients began experiencing severe complications such as polyester mesh erosion through the vaginal wall, vaginal infections, vaginal discharge, vaginal bleeding, foul odor and dyspareunia. In January 1999, Boston Scientific Corporation, ProteGen's manufacturer, recalled the product due to the unusually high number of complications. In the December 1999 edition of *The Journal of Urology*, a group of respected urologists from across the United States reported their findings on those complications. These findings included a high rate of complications such as tissue erosion and urethral erosion among patients in whom the ProteGen sling was placed.

During the TVT-Retropubic's FDA submission process in the late 1990s, Ethicon used the ProteGen® sling as its predicate device despite the problems and ultimate recall discussed above.

2. Mentor ObTape®

The ObTape® bladder sling was introduced in 2003 by the Mentor Corporation. The ObTape mesh sub-urethereal sling is a medical device, which was inserted through via a surgical procedure via the transobturator route for the treatment of female stress urinary incontinence.

ObTape bladder sling was used in around 36,000 women prior to its elimination from the medical device market in 2006 due to its high rate of complications. Although the Ob Tape mesh was presented as a permanent solution, a large number of women have experienced debilitating complications associated with their ObTape treatment. A 2007 study showed that over 20% of ObTape recipients experienced the extrusion of the sling through the vaginal walls [Siegal et al]. Other patients developed vaginal discharge, as well as pain during sexual intercourse as well as pelvic abscesses. Originally, it was assumed that problems with the ObTape sling stemmed from the mistakes of doctors. However, subsequent findings showed that the ObTape sling had an inherent design defect due to its use of overly dense and non-woven sling material. ObTape mesh erosions into the urethra can also result in the excretion of blood and urine. Initially, mesh erosion is typically treated with a cream prescribed by a doctor; but in many cases, the cream will not fix the mesh complication. In many mesh erosion instances, further surgery may be required to remove the mesh implant. Removal of the ObTape mesh sling may be successful in treating mesh erosion, but in some situations, even after multiple surgeries, there may be persisting complications due to mesh erosion.

3. TVT – Retropubic

The Gynecare TVT device is intended to be used as a pubovaginal suburethral sling for treatment of female stress urinary incontinence (SUI), caused by from urethral hypermobility and/or intrinsic sphincter deficiency. Gynecare TVT introducer, rigid catheter guide and Gynecare TVT abdominal guides and couplers are available separately and intended to facilitate the placement of the Gynecare TVT device. The reusable TVT handle and rigid catheter guide are also used to facilitate device placement.

The components to the TVT-Retropubic procedure are the TVT device, the polypropylene mesh sling attached to needles, TVT Introducer and the TVT Rigid Catheter Guide.

4. TVT-Device and Prolene Mesh Sling

The TVT device is a sterile single-use device consisting of one piece of undyed Prolene® polypropylene mesh (tape) approximately 1/2 x 16 inches (1.1 x 40 centimeters), covered by a plastic sheath cut in the middle, and held between two stainless steel needles bonded to the mesh and sheath with plastic collars. The Prolene mesh is constructed of knitted filaments of extruded polypropylene strands identical in composition to that used in Prolene polypropylene nonabsorbable surgical suture. The mesh is approximately 0.027 inches (0.7 millimeters) thick. This material "when used as a suture" has been reported to be "non-reactive and to retain its strength indefinitely" in clinical use. According to the Ethicon IFU, the Prolene mesh is knitted by a process "which interlinks each fiber junction and which provides for elasticity in both directions. This bi-directional elastic property allows adaptation to various stresses encountered in the body."[1]

5. TVT introducer

The TVT introducer is a non-sterile and reusable surgical tool for the TVT-Retropubic procedure. The introducer is constructed of stainless steel. It consists of three parts; a handle, an inserted threaded metal shaft and a synthetic rubber 0-ring. The rubber 0-ring prevents the shaft from falling out from the handle when the introducer is held upside down during surgical use. The introducer is intended to facilitate the passage of the TVT device from the vagina to the abdominal skin. It is connected and fixed to the needle, via the threaded end of the shaft, prior to inserting the needle with the tape.

6. TVT Rigid Catheter Guide

The TVT Rigid Catheter Guide is a non-sterile, reusable instrument intended to facilitate

[1] ETH.MESH.00353639, ETH.MESH.00015699 –00015706; ETH.MESH.00013506; ETH.MESH.00922443-00922445; ETH-00938; Walji Deposition p471-472; Robinson Deposition 3-14, p683-684; Kirkemo Deposition 4-18, p246-247, Ciarrocca Deposition 3-29, p264

the identification of the urethra and the bladder neck during the surgical procedure. It is inserted into a Foley urinary catheter.

7. Surgical Technique

A small anterior vaginal wall incision with lateral dissection is made under the midurethra as well as two suprapubic skin incisions. After the introducer is attached to the end of one of the needles, the device is passed paraurethrally penetrating the urogenital diaphragm passing closely behind the pubic bone up to the abdominal incision. Insertion and passage are controlled by using one finger in the vagina under the vaginal incision and fingertip control on the pelvic rim. Via use of a Foley catheter and the rigid catheter guide, the urethra and empty bladder are moved contralateral to the side of the needle passage. The procedure is then repeated on the other side. After passage of the needles, cystoscopy is performed to confirm bladder integrity. The needles are pulled upward to bring the tape (sling) loosely (i.e., without tension) under the midurethra. The needles are then separated by cutting from the tape. The plastic sheaths that surround the tape are removed. By using patient feedback (e.g., coughing with a full bladder), appropriate tension on the sling is supposed to be determined taking care to avoid over-tensioning. During this test, the vaginal incision should temporarily be closed by a gentle grip with a small forceps. Following this procedure, catheterization is not typically required.

C. The Old Construction Heavy Weight/Small Pore Mechanically Cut Polypropylene Mesh in the TVT Should Not Be Used in the Pelvic Floor

Because of the defective characteristics of the TVT discussed below and throughout this report, Ethicon fell below the standard of care of a reasonable and prudent medical device manufacturer. The old construction mechanically cut and laser cut mesh used in the TVT device should not be used in the pelvic floor because the risks of the device far outweigh the benefits of the device. The inadequacies of the mesh and the TVT lead to long term complications,

including but not limited to, pain, acute and chronic pelvic pain, vaginal pain, permanent dyspareunia, injury and pain to partner during sexual intercourse, negative impact on sexual function, the risk of multiple pelvic erosions that can occur throughout one's lifetime, vaginal scarring, vagina anatomic distortion, inability to remove the device, permanent risks for erosions, the need for multiple surgical interventions that carry with them significant risks of morbidity, the development of worsening incontinence and urinary dysfunction including urinary urgency, urinary urge incontinence, urinary retention, suprapubic pain, suprapubic numbness, pain with lifting, pain with ambulation, and pain with sitting.

1. The mesh in the TVT is not inert and degrades

As polypropylene has been used in surgery for over 50 years as a suture material, Ethicon marketed the mesh in TVT as inert. However, many published studies and internal Ethicon studies and documents show that the mesh is not inert and does degrade.[2] In 1987, Ethicon tested samples of explanted Prolene mesh made from the same material as the TVT mesh.[3] After 8 years of implantation, the testing showed that the mesh was severely cracked. In 1992, Ethicon completed a study where Prolene sutures were implanted in beagle dogs for up to seven years. These sutures were removed from the dogs and examined by Ethicon's own scientists, who

[2] ETH. MESH.08315783 2012 + M CER: Reduction of the mass [of the implant] and the increase in the pore size of the mesh implant foreign body are seen to alter the inflammatory response which in turn is likely to alter tissue ingrowth... As the mass of the mesh implant is reduced and the pore size is increased the surface area exposed to the host is reduced, and the foreign body reaction to the implant is reduced."; ETH.MESH.02589033 - 02589079; ETH-80645 – 80651; Robinson Deposition 3-13, p 120; Hinoul Deposition 4-5, p165-170; Robinson Deposition 3-13, p129-130; Kirkemo Deposition 4-18, p138; 84 Klinge U, Klosterhalfen B, Muller M et al: Foreign body reaction to meshes used for the repair of abdominal wall hernias. Eur J Surg. 1999 Jul;165(7):665-73. Klinge U, Klosterhalfen B, Birkenhauer V: Impact of polymer pore size on the interface scar formation in a rat model. J. Surgical Research 103, 208-214 (2002). Klinge U, Klosterhalfen M, Muller A et al: Shrinking of polypropylene mesh in vivo: an experiment study in dogs. European Journal of Surgery Volume 164, Issue 12, pages 965–969, December 1998.; Klosterhalfen B, Klinge W, Schumpelick V: Functional and morphological evaluation of different polypropylene-mesh modifications for abdominal wall repair. Biomaterials. 1998 Dec;19(24):2235-46.; Klosterhalfen B, Klinge W, Hermanns B et al: Pathology of traditional surgical nets for hernia repair after long-term implantation in humans. [ABSTRACT] Chirugr 2000;71:43-51.; Klosterhalfen B, Junge K, Klinge W. The lightweight and large porous mesh concepts for hernia repair. Expert Rev Med Devices. 2005 Jan;2(1):103-17. Clave A, Yahi H, Hammou J, et al. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 patients. Int Urogynecol J. 2010 Mar;21(3):261-70. Klinge et al The Ideal Mesh Klosterhalfen et al: Retrieval study at 623 human mesh explants made of polypropylene. Kwon Inflammatory Myofibroblastic tumor Birolini Mesh Cancer Sternschuss Post implantation alteration of polypropylene in humans ETH.MESH.02091873 -- abnormal chronic toxicity and doing nothing

[3] ETH.MESH.12831407

found surface degradation in many of the samples after 7 years of implantation.[4] Ethicon scientist and corporate spokesperson, Thomas Barbolt, agreed that surface degradation can occur with the TVT mesh, and that this fact was confirmed by the Ethicon studies.[5]

Further evidence that polypropylene mesh degrades over time was provided in 1998 by the publication of the Mary article, who studied the phenomenon of mesh degradation, and concluded the process of polypropylene cooling, where the polypropylene strand cools first on the inside and then on the outside can make the strand more susceptible to degradation on the outside.[6] In 2007, Costello et al., reported that polypropylene is more susceptible to degradation due to oxidation caused by inflammatory response. Using Scanning Electron Microscopy (SEM), degradation could be seen in polypropylene in the form of cracks and peeling.

Dr. Donald Ostergard, urogynecologist and founder of AUGS, created a presentation titled "Polypropylene is Not Inert in the Human Body" in which he described degradation of in vivo polypropylene.[7] Dr. Ostergard concluded that Prolene mesh degradation occurs by oxidation. He further concluded that a large surface area, such a piece of surgical mesh, in contrast to a suture, incites more inflammation and results in more oxidation since more macrophages are present. These macrophages then secrete hydrogen peroxide and hypochlorous acid to oxidize the mesh, which can cause the mesh to become brittle and to crack. As discussed below, these changes cause complications to patients due to the increased inflammatory response.

In a 2010 article by Clave et al., 100 explants were analyzed. Results showed a greater than 20% rate of degradation from the implants. They concluded that "for transvaginal surgery, clinical experience indicates the use of low density, large pore implants knitted from a

[4] ETH.MESH.05453719
[5] Deposition of Thomas Barbolt, January 8, 2014, pg 409:2-13; 516:21-517:4
[6] Mary, Celine, et. al. Comparison of In Vivo Behavior of Polyvinylidene Fluoride and Polypropylene Sutures used in Vascular Surgery
[7] "Polypropylene is Not Inert in the Human Body" Presentation by Donald R. Ostergard

monofilament to facilitate tissue integration, and decrease the inflammatory response….not all types of PP implants degraded equally." It should be noted that the lead author, Henri Clave, holds an educational position for Ethicon Europe. In fact, Ethicon's scientists responded to that article, admitting that it was possible that the polymers may be subject to surface degradation free radicles and oxygen species in the human body, but that it did not know the clinical significance of these reactions. [8] Later, in 2013, the Wood study showed that polypropylene explanted from a patient showed significant oxidation of the material, and concluded that polypropylene will degrade in an oxidizing environment, such as a foreign body response in the human body.[9] Other authors and studies have demonstrated similar results with polypropelene in general.[10] In 2015, seven explants from sling devices including the TVT, were removed 4-7 years after implantation. Comparison of SEM images for explant samples with control pristine samples reveled extensive surface degradation and the formation of surface cracks in the samples, demonstrating the polypropylene fibers from mid-urethral slings are not inert over time.[11]

As polypropylene degrades, the inflammatory response increases and intensifies. The abraded fiber surface increases the surface area of the mesh, provides multiple areas that can effectively harbor bacteria, become brittle and creates a "barbed-wire" effect, all of which lead to

[8] ETH.MESH.07205369
[9] Wood, et. al. Materials characterization and histological analysis of explanted polypropylene, PTFE, and PET hernia meshes from an individual patient. J Mater Sci: 24:1113-1122 (2013).
[10] Iakovlev, et al., Pathology of Explanted Transvaginal Meshes. Intl . Science Index Vol. 8 No. 9 (2014); Martin, MK Gupta, JM Page, F Yu, JM Davidson, SA Guelcher, CL Duvall. Synthesis of a Porous, Biocompatible Tissue Engineering Scaffold Selectively Degraded by Cell-Generated Reactive Oxygen Species. Biomaterials 35(12):3766-76, 2014; AE Hafeman, KJ Zienkiewicz, AL Zachman, HJ Sung, LB Nanney, JM Davidson, SA Guelcher. Characterization of degradation mechanisms of biodegradable lysine-derived aliphatic polyurethanes. Biomaterials 32(2):419-29, 2011.
[11] Tzartzeva, et al. In-depth nano-investigation of vaginal mesh and tape fiber explants in women. Abstract 366 (2015);

an increased risk of an enhanced and chronic inflammatory response, as well as chronic infections due to bacterial proliferation at the mesh surface.[12]

The literature and internal Ethicon studies demonstrate that Ethicon's surgical polypropylene meshes oxidize, degrade, crack and peel in human tissue and become brittle. Dr. Iakovlev has also published numerous articles showing and explaining the degradation and surface cracking of polypropylene explants using histological and transmission electron microscopy approaches.[13]

Ethicon also knew this information before and at the time of launch of the TVT. There are Ethicon studies dating back as far as 1983 using test methods nearly identical to Dr. Iakovlev's showing in vivo degradation of the Prolene polypropylene material.[14] Ethicon conducted additional studies in 1985 (dog study) and in 1987 (human explants); both showing in vivo degradation and cracking of the polypropylene materials.[15] In fact, Ethicon had its meshes reviewed by an outside consulting company who found that its meshes degrade and that the process starts immediately.[16] Yet, Ethicon never performed a study to determine the clinical significance of the degradation of its mesh.

It is my opinion, to a reasonable degree of medical and scientific certainty that polypropylene degrades in the human body causing the complications discussed throughout this report to women.

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[12] [Mamy L, Letouzey V, Lavigne J et al: Correlation between shrinkage and infection of implanted synthetic meshes using an animal model of mesh infection. Int Urogynecol J. 2011 Jan;22(1):47-52.]
[13] Iakovlev V, Guelcher S, Bendavid R. In Vivo Degradation of Surgical Polypropylene Meshes: A Finding Overlooked for Decades. Virchows Archiv 2014, 463(1): 35; Iakovlev V, Guelcher S, Bendavid R. In Vivo Degradation of Surgical Polypropylene Meshes: A Finding Overlooked for Decades. Virchows Archiv 2014, 463(1):35.
[14] ETH.MESH.15955438
[15] ETH.MESH.00004755; ETH.MESH.11336474; ETH.MESH.13334286
[16] ETH.MESH.07192929

2. The TVT mesh is Heavyweight and Small Pore causing increased tissue response, chronic inflammatory response, contraction and shrinkage of the mesh, fibrotic bridging and scar plate formation, and folding and curling of the mesh

Ethicon scientists have known for over 16 years that heavyweight, small pore meshes are associated with excessive foreign body reaction, chronic inflammation, bridging fibrosis, scar plate formation, and consequential shrinkage of the mesh.[17] Further, Ethicon knew that the TVT mesh is heavyweight and has small pores.[18] Ethicon has realized the need for decreasing complications rates from its heavyweight, small pore meshes through the development of lighter weight materials, which elicit a lower inflammatory response in the human body.[19] In fact, Ethicon has developed lighter weigh materials for use elsewhere in the human body, including the pelvic floor. However, today, Ethicon continues to use the heavyweight, small pore Prolene mesh, originally developed in 1974 for use in hernia surgery, for its TVT device used for SUI.[20] This is true despite the fact that Ethicon knows the heavyweight, small-pore meshes have a greater inflammatory response and is related to increased rates of patient complications than lightweight large pore meshes regardless of where the mesh, is located in the human body.[21]

The implantation of the TVT mesh creates a foreign body reaction and a chronic inflammatory response that can lead to chronic pain in the patient. The body's foreign body response to the mesh can cause a severe and chronic inflammatory reaction leading to excessive scarring in and around the mesh and the degree of this reaction is directly related to the weight

[17] ETH.MESH.05479411; Klinge U., Klosterhalfen B., Birkenhauer V., Junge K., Conze J., and Schumpelick V., Impact of Polymer Pore Size on the Interface Scar Formation in a Rat Model; Cobb W, Kercher K, Heniford T. The Argument for Lightweight Polyropylene Mesh in Hernia Repair. Surgical Innovation. 2005; 12(1):T1-T7; Cobb, W., et al. Textile Analysis of Heavy Weight, Mid-Weight, and Light Weight Polypropylene Mesh in a Porcine Ventral Hernia Model. Journal of Surgical Research 136, 1-7 (2006); Klinge U, Klosterhalfen B, Muller M, Ottinger A, Schumpelick V. Shrinking of Polypropylene Mesh in vivo: An Experimental Study in Dogs. Eur J Surg. 1998: 164; 965-969; Klosterhalfen, B., Junge, K., Klinge, U.The lightweight and large porous mesh concept for hernia repair. Expert Rev. Med. Devices. 2005; 2(1)

[18] ETH.MESH.05479411, Cobb et. al., The Argument for Lightweight Polypropylene Mesh in Hernia Repair, Deposition of Joerg Holste, July 29, 2013 40:12-15, Deposition of Brigette Hellhammer MD., September 11, 2013 151:16-20, ETH.MESH.05479535

[19] ETH.MESH.01203957, Trial Testimony of Piet Hinoul, Batiste March 27, 2014 afternoon, 73:11-25

[20] ETH.MESH.04941016, HMESH_ETH_02030355,

[21] Deposition of Joerg Holste, July 29, 2013 95:4-11

and pore size of the mesh device.[22] [23] [24] [25] Ethicon has known that clinical data have shown more chronic pain with heavyweight meshes such as the TVT mesh, than with lightweight, partially absorbable meshes. Ethicon's own medical director has stated that the presence of the foreign body, i.e. the TVT mesh, can be responsible for chronic pain syndrome in the patient.[26] In fact, one study has found that heavyweight meshes with small pores had to be explanted due to chronic pain more frequently than lightweight meshes with large pores.[27]

The foreign body reaction caused by the TVT mesh is chronic and this chronic inflammation and reaction can lead to mesh contraction and shrinkage.[28] Most studies show less shrinkage than heavyweight meshes, and pore size is one of the most important factors regarding mesh shrinkage.[29] Ethicon knew that all polypropylene meshes experience a 20-50% reduction in their initial size following implantation in the body.[30] Ethicon's medical director knew that the TVT mesh can shrink, and generally believed the TVT mesh would shrink approximately 30% post implantation.[31] The mesh contraction and shrinkage can increase the degree of foreign body reaction and mesh degradation, increasing the degree of pelvic pain and pelvic floor dysfunction such as sexual activity and urination, pain with sitting, and ambulation.[32]

A recent study has shown that mesh shrinkage is progressive and there is a linear evolution of the contraction rate over time, indicating that mesh contraction continues in the

[22] Deposition of Piet Hinoul, April 4, 2012 99:99-99:25
[23] ETH.MESH.08315782
[24] Trial Testimony Piet Hinoul, March 27, 2014 afternoon, 27:10-17
[25] ETH.MESH.05916450
[26] ETH.MESH.01202102
[27] Klostherhalfen,B, Junge, K, Klinge, U, "The lightweight and large porous mesh concept for hernia repair," Expert Rev. Med. Devices, 2005 2(1)
[28] Deposition of Christophe Vailhe June 21, 2013 838:8-19
[29] ETH.MESH.02316781
[30] Cobb W, Kercher K, Heniford T. The Argument for Lightweight Polyropylene Mesh in Hernia Repair. Surgical Innovation. 200
[31] ETH.MESH.03910418
[32] De Tayrac, et. al. Garcia M, Ruiz V, Godoy A, et al: Differences in polypropylene shrinkage depending on mesh position in an experimental study. American Journal of Surgery Vol 193, Issue 4, April 2007, p538-542

patient's body indefinitely into the future.[33] Vaginal mesh contraction can result in vaginal fibrosis, infection, chronic vaginal pain, chronic pelvic pain, vaginal shortening, vaginal narrowing, vaginal extrusion, adjacent organ erosion, and dyspareunia. Feiner and Maher evaluated 17 women with vaginal mesh contraction to demonstrate that the mesh caused the condition. The patients' presenting complaints included severe vaginal pain, dyspareunia, and focal tenderness over contracted portions of mesh on vaginal examination, mesh erosion, vaginal tightness, and vaginal shortening. The patients underwent surgical intervention with mobilization of mesh from underlying tissue, division of fixation arms of the central graft, and excision of contracted mesh. Fifteen of 17 (88%) patients reported a 'substantial reduction in vaginal pain following explantation, while none of 11 (64%) reported 'substantial' reduction in dyspareunia. However, despite Feiner's relative success with mesh explantation, the adverse effects of transvaginal mesh contraction caused permanent life-altering sequelae in 22-46% of patients in this study.[34] I personally see this type of permanent life-altering sequelae in my daily practice in patients I treat for severe complications related to mesh slings, including Ethicon's TVT device.

Polypropylene induces a rapid and acute inflammatory response and a strong scar formation. Heavyweight meshes with small pores such as the mesh in the TVT, induce an intense, chronic foreign body reaction with intensified bridging scar formation.[35] An increased foreign body reaction with a chronic inflammatory response and the forming of a rigid scar plate are the primary reasons for the shrinkage and contraction of meshes. Decreasing the weight of

[33] Mamy L, Letouzey V, Lavigne J et al: Correlation between shrinkage and infection of implanted synthetic meshes using an animal model of mesh infection. Int Urogynecol J. 2011 Jan;22(1):47-52.;
[34] Feiner B, Maher C. Vaginal mesh contraction: definition, clinical presentation, and management. Obstet Gynecol. 2010 Feb;115(2 Pt 1):325-30.;
Foon R, Toozs-Hobson P, Latthe P. Adjuvant materials in anterior vaginal wall prolapse surgery: a systematic review of effectiveness and complications. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Dec;19(12):1697-706.
[35] ETH.MESH.02316781

these meshes reduces both shrinkage and the inflammatory response. A pore size of greater than 1 mm is needed to prevent the fibrotic bridging and scar plate formation.[36] The mesh in the TVT has a pore size that is less than 1mm after implantation.[37] The fact that the pore size of the TVT is not greater than 1mm in all directions prevents proper tissue integration, which can reasonably be expected to result in the development of a rigid scar plate, leading to, among other things, the potential for increased erosion, pain, nerve entrapment, and dyspareunia.

Ethicon knew as early as 1998 that the construction and weight of the Prolene mesh utilized in the production of the TVT needed to be improved due to the fact that the mesh curled and folded under tension and would not return to its original shape, remaining curled.[38] Ethicon embarked on the "Prolene Mesh Improvement Project" to address these problems with the mesh. Ethicon ultimately changed the original, heavyweight 1974 mesh used for flat hernia repairs by (1) changing the construction of the mesh to prevent the mesh from curling up under tension, and (2) changing the size of the fiber used in the mesh from a 6 mil fiber to a 5 mil fiber, making the mesh lighter weight.[39] Despite these improvements to the Prolene flat hernia mesh, Ethicon continues to use the original construction, heavier weight 6 mil Prolene mesh in the TVT product. This is true even though Ethicon knows that mesh curls under tension, and that the mesh is known for its "bad curling quality."[40] Even though the initial long-term intent of the mesh improvement project was to replace the TVT mesh with the improved construction,

[36] ETH.MESH.01785259; ETH.MESH.02316781; ETH.MESH.02148431 Klosterhalfen B, Junge K, Klinge W. The lightweight and large porous mesh concepts for hernia repair. Expert Rev Med Devices. 2005 Jan;2(1):103-17; Batke deposition 08/01/012 113:3 to 114:3, 172:6 to 174:15, 118:10 to 120:25;Hellhammer deposition 09/12/13 403:18 to 404:9; 407:13-23; Holste depositions 07/29/13 51:3 to 53:6; Holste Deposition 12/14/12 89:20 to90:21; Semin Immunopathol (2011) 33:235–243 - a Scar net formation following large pore (~3 mm) and b scar plate formation following small-pore (~0.3 mm) mesh implantation; Arnaud deposition 9/25/13 756:9 to 757:8; ETH.MESH.03021946 T-Pro Stage Gate Meeting on August 25, 2008; ETH.MESH.02587926 When the Implant Worries the Body; ETH.MESH.01752532: Mesh Design Argumentation Issues; ETH.MESH.01785259 January 17, 2010 Email re; +M relaxation; ETH.MESH.04941016 Lightweight Mesh Development
[37] ETH.MESH.08315783;
[38] ETH.MESH.09264945
[39] ETH.MESH.10603246, HMESH_ETH_00782152
[40] ETH.MESH.02182839, HMESH_ETH_02030355

lightweight mesh,[41] Ethicon did not use the improved material because it felt that the changed mesh would "obsolete the clinical data" they already had on the TVT product, which was a competitive advantage for the company.[42] An illustration of the TVT Prolene mesh curling after being placed under tension can be seen below.

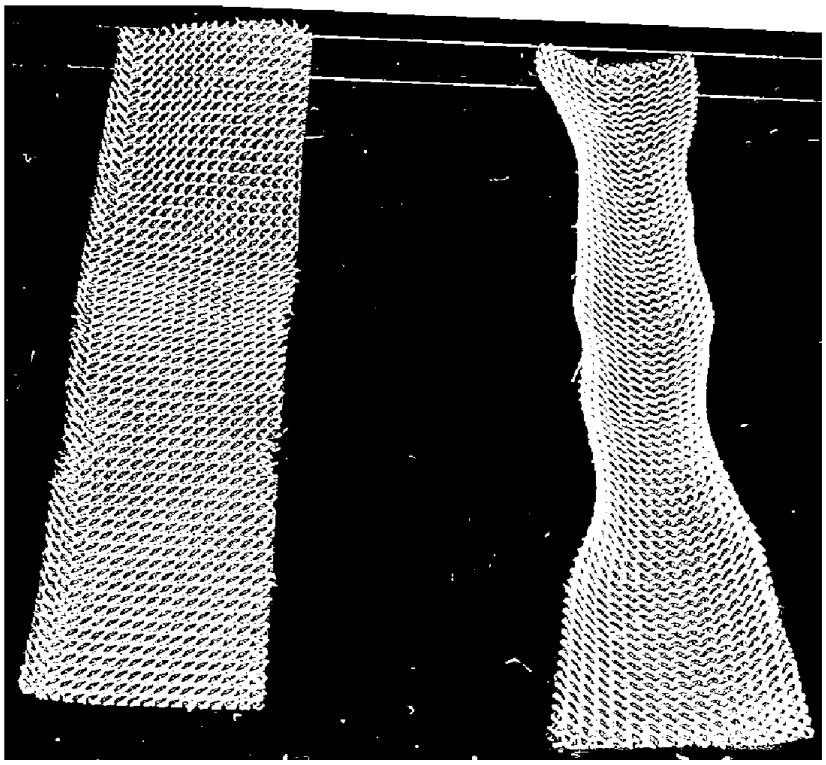
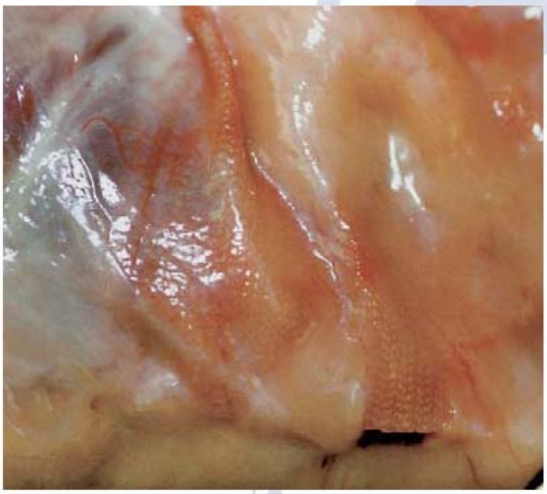


Figure 1 – Control mesh sample before and after the application of the force. A clear picture of mesh curling results.

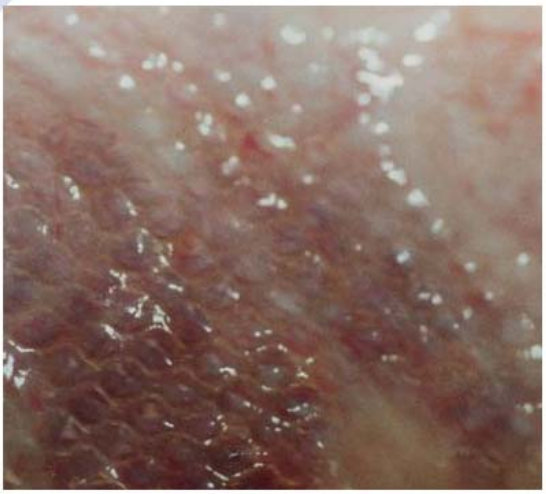
Ethicon is also aware that the heavyweight, small pore nature of the Prolene mesh makes it more likely than lightweight, large pore, partially absorbable mesh materials to "fold up" following implantation. This folding up of the mesh has also been referred to as the "potato chip" phenomena, which is caused by the increased inflammatory response to the increased

[41] ETH.MESH.09264884
[42] ETH.MESH.03911107

weight and small pores of the current mesh.[43] Lightweight, large pore meshes tolerate compression much better than heavyweight Prolene mesh, which has pronounced edges and crumpling during tissue integration.[44] This folding of the mesh increases the amount of scar tissue formation and increases the likelihood of fibrotic bridging and scar plate formation of the mesh. In fact, in its 2004 product catalog, Ethicon advertised that its lighter weight, larger pore Vypro mesh had 60% less foreign body material compared to the Prolene mesh, and was less susceptible to the development of folded mesh post-implantation.[45]



Traditional polypropylene mesh. 90 days post-implantation. Fold development (in-vivo study)



Lightweight VYPRO* II mesh. 90 days post-implantation. Fold-free incorporation (in-vivo study)

3. Ethicon's cutting process made the mesh even more dangerous

For Ethicon's mesh that is mechanically cut, fraying is inherent in the design of the device.[46] Stretching increases the probability of fraying, and when fraying occurs, the mesh narrows in places and particles break off and are lost from the mesh.[47] These defects in the mesh

[43] ETH.MESH.05918776
[44] ETH.MESH.05446129
[45] Ethicon 2004 product catalog
[46] ETH.MESH.00541379
[47] ETH.MESH.00541379

related to the mechanical cutting process lead to increased urinary retention, erosions, extrusions and exposures of the mesh into vaginal tissues, and particles of the mesh migrating into surrounding vaginal tissues causing pain.

Ethicon performed testing on TVT mechanically cut mesh samples where the mesh was stretched to 50% elongation and then measured for particle loss. Ethicon performed this test because based on their experience, 50% elongation was the estimated amount of force that is placed on the mesh during implantation.[48] In fact, one of Ethicon's Senior Engineers, Gene Kammerer stated that "it is my experience, after viewing many surgical procedures and performing numerous procedures on cadavers myself, that the mesh stretches approximately 50% at the maximum." [49] Testing done by Ethicon in 2002 showed that after elongation, some test articles lost up to 18% of their weight from particle loss.[50] A study published in 2004 by Pariente found that the TVT sling lost 8.5% of its particles during testing, more than 5 other competing slings.[51] Another researcher found the TVT easily deforms when tensioned under the urethra, which results in fraying or tanged edges and thinning of the mesh.[52] In fact, fraying during elongation was a major complaint of customers,[53] and was critical to the quality of the TVT device.[54] Physicians told Ethicon that particle loss from implanted mesh can migrate through vaginal tissues and cause pain.[55] The reason for the laser cut mesh project was to eliminate or reduce the release of these particles.[56]

[48] ETH.MESH.01824104, ETH.MESH.00584811, ETH.MESH.00301874
[49] ETH.MESH.00584811; ETH.MESH.08334244
[50] ETH.MESH.04384185
[51] ETH.MESH.01221055, Pariente et.al., An independed biomechanical evaluation of commercially available suburetheral slings.
[52] Moali et.al., Tensile properties of five commonly used mid-urethral slings relative to the TVT. Int Urgynecol J June 22, 2007
[53] ETH.MESH.10611169
[54] ETH.MESH.00301741
[55] ETH.MESH.05644164, ETH.MESH.03924557
[56] ETH.MESH.00301741

Ethicon continued to see problems with inconsistent tape width.[57] Doctors would report that the edges of the tape were crumbling, and that it got worse if the tape was stretched.[58] Ethicon knew that the mechanically cut mesh was more likely to curl and rope which reduces the area of mesh to a localized point, increasing the pressure and potentially causing urinary retention.[59] Ethicon also knew that the increased roping or deconstruction of the mesh knit due to the narrowing of the mesh could result in erosion.[60] In 2005, Ethicon tested laser cut mesh for the TVT and again performed a 50% elongation test of the material and compared that side by side with the mechanically cut mesh. [61] Ethicon found that that the laser cut mesh substantially reduced the roping, curling, fraying and particle loss they were seeing with the mechanically cut mesh.[62] However, as discussed below, laser cutting of the mesh introduced new and different problems.

The roping and fraying of the mechanically cut mesh results in increased particle loss and frayed and sharp edges, which result in erosions, extrusions, and exposures of the mesh into the vaginal tissue of patients causing pain, chronic pain, and dyspareunia. These problems, along with numerous other complications, are things I see on a daily basis in my clinical practice dealing with mesh complications, including Ethicon's TVT device. Ethicon has known that it was important to have a mesh that did not fray or have "spiky" or sharp edges in 1997 before the TVT product was even launched in the United States, when it was reported to Ethicon that a patient treated with Prolene had a vaginal erosion requiring trimming of the mesh.[63] Ethicon also

[57] ETH.MESH.12002601
[58] ETH.MESH.02180833
[59] ETH.MESH.01822361
[60] ETH.MESH.06696593
[61] ETH.MESH.08334244-45
[62] ETH.MESH.00526473
[63] ETH.MESH.12006257

knew that ideally, the Prolene mesh should have a smooth edge,[64] and that the mesh in the TVT should minimize abrasion.[65] Ethicon received multiple reports from patients of frayed mesh extruding through vaginal tissues causing pain both for women and their sexual partners.[66] The laser cut mesh created smooth or beaded edges in contract to the sharp, spike-like edges of the mechanically cut mesh,[67] which reduced the possibility of vaginal erosion.

In 2005, Ethicon introduced laser cut mesh which decreased the likelihood of fraying mesh and in turn, substantially decreased the likelihood of these adverse events; yet Ethicon continued to sell the mechanically cut mesh for the TVT despite laser cut mesh being a safer option from the point of view of over-tensioning defects and complications. However, the laser cut mesh created another set of problems. In part due to the beaded edge, the laser cut mesh had different mechanical properties as compared to the mechanically cut mesh. Specifically, the laser cut mesh was stiffer, less flexible, and less elastic than the mechanically cut mesh.[68] These essential mesh properties affect how a plastic mesh performs when being implanted in the pelvic floor and change how much force the surgeon should use when implanting the mesh and setting the appropriate tension. As previously discussed, the tension in an implanted mesh can lead to complications such as pain, erosion, and damage to tissues and organs. Ethicon never warned doctors that the new laser cut mesh had different mechanical properties than the mechanically cut mesh. Instead, Ethicon assured doctors that the laser cut mesh was identical to the mechanically cut mesh.

Despite the fact that Ethicon introduced the option of laser cut mesh for the TVT in 2006, they continued to offer the mechanically cut mesh for financial reasons. The primary motivator

[64] ETH.MESH.09266457
[65] ETH.MESH.12009276
[66] ETH.MESH.02620914-02620917; ETH.MESH.02620964-02620968, 02621143-02621146, 02622276-02622279,
[67] ETH.MESH.09656790-09656795
[68] Deposition of David Robinson, MD, July 25, 2013 at 507:18-508:1 & 509:6-21

for continuing to sell the mechanically cut mesh was that they did not want to make obsolete the years of clinical data that were already available on the TVT.[69] In fact, Ethicon employees were reluctant to change the mesh at all because they wanted to continue to rely on the clinical data already established, most notably the Ulmsten/Nilsson series of clinical studies.[70] Ethicon instead chose to allow both meshes to "ski on the market" with the mechanically cut mesh being offered as the "Colonel's original recipe" in order to maximize the sales of the product, initially only offering the laser cut mesh to those customers who asked for it. [71]

As a result of all of the defects and problems with the mesh in the TVT discussed above, the TVT device should not be implanted into the human body for use in the treatment of SUI. These defects and problems with the mesh lead to numerous injuries, including but not limited to pain, acute and chronic pelvic pain, vaginal pain, permanent dyspareunia, injury and pain to partner during sexual intercourse, negative impact on sexual function, the possibility of multiple pelvic erosions that can occur throughout one's lifetime, vaginal scarring, vagina anatomic distortion, inability to remove the device, permanent risks for erosions, need for multiple surgical interventions, development of worsening incontinence and urinary dysfunction including urinary urgency, urinary urge incontinence, urinary retention, suprapubic pain, suprapubic numbness, pain with lifting, pain with ambulation, and pain with sitting.

4. Ethicon's Prolene Mesh tested positive for Cytotoxicity

Cytotoxicity is the quality of being toxic to cells. If a woman's tissues or organs are exposed to a cytotoxic substance, the cells can undergo necrosis and die rapidly, or they can undergo a form of controlled "cell death," known as apoptosis[72] It is my understanding that it is common for medical devices to be subjected to Cytotoxicity testing before they are marketed to

[69] ETH.MESH.03911107
[70] Deposition of Brigette Hellhammer, MD, September 11, 2013 120-121; Deposition of Axel Arnaud, MD., July 19, 2013 35-37.
[71] ETH.MESH.00526473, ETH.MESH.00687820
[72] About Apoptosis. Apoptosis Interest group, National Institute of Health, November 13, 2009

doctors and patients. In support of its application to market the TVT in the United States, Ethicon did not perform any controlled clinical studies to determine the Cytotoxic potential of the TVT prior to marketing the device, but instead determined that the "long term clinical experience with PROLENE mesh indicated that Cytotoxicity testing would be sufficient to support the biocompatibility of this [mesh] component."[73] Prior to the marketing the TVT device, the Prolene mesh had primarily been used in abdominal hernia repair, and had never before been specifically indicated for use in vaginal tissues. As a result, Ethicon's conclusion that no new clinical or animal studies were needed to evaluate the Cytotoxic potential of the TVT mesh is questionable at best.

In fact, to this day, I am not aware of any long-term studies undertaken by Ethicon to determine whether or not the TVT mesh is clinically cytotoxic in women.[74] However, early clinical studies indicated that the TVT mesh did indeed have cytotoxic potential. Notably, the 2004 Wang study reported a defective healing rate of 2.2% in a series of 670 patients, and a persistent defective healing rate of 1%[75]. While this study was not published until 2004, Ethicon had been advised that Dr. Wang had experienced 25 erosions from the TVT mesh, which he suspected was due to the body's rejection of the Prolene mesh in 2002.[76]

The initial Cytotoxicity testing of the TVT prototype device was conducted in March of 1997, and tested all components of the device together for a period of 24 hours. The results of this test indicated the mesh was severely cytotoxic.[77] Ethicon's own Scotland lab performed follow-up testing, this time testing the needle, heat shrinking tube, sheath, and polypropylene mesh separately. In this test, the polypropylene mesh in the TVT again tested positive for

[73] ETH.MESH.08476210
[74] Dr. David Robinson deposition, September 11, 2013, 1101:24-1102:5
[75] Wang AC, et. al. A histologic and immunohistochemical analysis of defective vaginal tape healing after continence taping procedures: A prospective case-controlled pilot study. American Jorunal of Obstetrics
[76] ETH.MESH.03736989, ETH.MESH.00409674
[77] ETH.MESH.06851860 at ETH.MESH.06852121

marked cytotoxicity. Ethicon did a third and final test in July of 1997, which finally provided a non-cytotoxic result for the polypropylene mesh. Ethicon relied on the results of this final, July 1997 test in support of its application to market the TVT device, and did not report the two prior positive cytotoxic test results to the FDA, surgeons, or the public. Ethicon's own Worldwide Medical Director from 2005-2010 was not aware of these positive tests during his tenure.[78] Notably, even the 1997 ISO elution testing showed that the polypropylene mesh in the TVT was moderate to severely cytotoxic, while the ISO agarose diffusion testing showed the mesh was non-cytotoxic. Despite the positive ISO elution testing, and the two previous tests showing the mesh was Cytotoxic, Ethicon concluded that "the long history of safe clinical use of polypropylene as a mesh and suture products suggests strongly that the material is inherently biocompatible, and the potential Cytotoxicity observed is self-limiting and minimal when compared to the implantation procedure itself."[79] It is my opinion that based on the 3 positive cytotoxic test results, that Ethicon failed in its duty as a reasonable medical device manufacturer by not conducting long-term studies to assess the Cytotoxic potential of the TVT mesh prior to marketing the device in women. This is particularly true in light of the fact that the Prolene mesh had never before been indicated specifically for use in vaginal tissues, and that there was only limited, short term data for 200 patients on a prototype device available at the time the device was first sold in the United States. In addition, the reports of 25 tape erosions from Dr. Wang in 2002 should have triggered an additional testing and assessment of the cytotoxic potential of the TVT mesh, but no additional cytotoxic testing was done as a result of these reports.

[78] Dr, David Robinson deposition, September 11, 2013, 1094:19-1095:1.
[79] ETH.MESH.08476210

I have seen the clinical effects of the cytotoxic potential of the TVT mesh in my practice. When I have removed Prolene TVT mesh from a patient with a mesh erosion, the tissue surrounding the mesh frequently shows evidence of necrosis and cell death. This type of necrosis is typically due to either: toxins, infections, trauma, or some combination of the three.

5. The TVT design is flawed because there is no way to properly tension the TVT device to lack of uniformity and it shrinks, ropes, curls and deforms making it too difficult to tension properly

Proper tensioning of the TVT device is critical to ensure that the device is successful in its intended use to cure stress urinary incontinence and to prevent complications. However, the design of the TVT device is flawed because Ethicon cannot properly determine and/or instruct surgeons on the proper placement of the device and, in fact, Ethicon provides contradictory instructions on tensioning in its instructions for use.

It is known that improper tensioning of the TVT can lead to failure of the procedure, urinary retention, and well as urinary obstruction.[80] The fact that the cough test was necessary to properly tension the mesh was noted by Dr. Ulmsten in his original 1996 publication on the TVT, as well as the co-inventor of the TVT, professor Nilsson, who noted that there was a 15% difference in success rates between patients treated with the TVT under local anesthesia with a cough test, and under general anesthesia, where no cough test was possible.[81] Despite being aware of this concern, Ethicon launched the TVT with an IFU that informed physicians that the procedure could be performed under general or local anesthesia, yet did not inform physicians that the success rate was much greater if performed under local anesthesia with a cough test.

[80] ETH.MESH.05222687
[81] ETH.MESH.0404851

Too much tension on the mesh can also lead to vaginal or urethral erosions.[82] In 2001, Ethicon medical directors recognized the need to have a standardized approach for tensioning the TVT and were working on a product which would avoid excessive tension on the mesh, but this product was never completed, and Ethicon never properly addressed how to instruct surgeons how to properly tension the mesh.

The IFU for the TVT provides insufficient and contradictory information on how to properly tension the TVT. In fact, Ethicon employees have acknowledged that the TVT has never truly been tension free, despite years of marketing it as such, and that they cannot accurately describe how to tension the mesh.[83] The IFU's Warnings and Precautions section cautions surgeons to "ensure that the tape is placed with minimal tension under the mid-urethra." Yet in the very same section, the surgeon is instructed to place the tape "tension-free" in the mid-urethral position to minimize the risk of de novo detrusor instability. Surgeons are told in the instruction section that once the tape is placed, they should pull the needles upwards "to bring the tape (sling) loosely, i.e. without tension, under the midurethra" and to adjust the tape so that leakage is limited to no more than one or two drops. The physician must put some kind of tension or force on the tape in order to limit the leakage.

The IFU's Adverse Reactions section says that over correcting, i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction, yet the surgeon has been previously provided with five conflicting and confusing instructions to place the tape with (1) minimal tension, (2) tension-free, (3) loosely, (4) without tension, and (5) to adjust the tail of the TVT mesh until leakage is limited.[84] This leaves the physician with no clear, articulable standard on how to void the serious adverse reaction of urinary retention or urinary

[82] ETH.MESH.05529653; ETH.MESH.0016113; ETH.MESH.05529274; ETH.MESH.04044797
[83] ETH.MESH.01784428; ETH.MESH..06861473
[84] TVT IFU

obstruction. Since it is generally impossible to adjust the tensioning more than 24 hours after an operation as tissue ingrowth begins to occur, a re-operation surgery is generally required to correct this adverse event. Therefore, it is particularly important for patient safety to determine and describe the proper tensioning of the device as part of the product design. In addition, IFU is silent of the fact that over tensioning can cause other adverse reactions as well, including vaginal or urethral erosion.

Moreover, Ethicon failed to inform that physicians that the mesh could shrink from 30-50% once the TVT was placed, which would affect the final placement and tensioning of the mesh, and failed to account for shrinkage in determining tensioning for the TVT.[85] Ethicon also failed to account for the effects that roping, curling, narrowing, and deformation of the mesh could have on tensioning. It is my opinion to a reasonable degree of medical certainty that Ethicon has failed in its duty as a reasonable medical device manufacturer by not developing and articulating clear and accurate instructions to surgeons on how to tension the mesh, rendering the device defective. It is also my opinion to a reasonable degree of medical certainty that Ethicon cannot develop and articulate clear and accurate instructions on how to properly tension the mesh as long as defects of heavyweight mesh shrinkage, roping, curling, narrowing, and deformation of the mesh exist as those defects create too many variations in the tensioning of the device to be overcome by instructions, no matter how well designed and articulated they may be.

6. The MSDS for the Prolene mesh states not to use with strong oxiders like peroxides which can be abundantly found in the vagina

The polypropylene mesh in the TVT is made from plastic pellets supplied by Sunoco, a petrochemical company. Included with these plastic pellets is a material safety data sheet,

[85] Ethicon knew that polypropylene mesh would likely shrink after implantation, and used 30% as a rule of thumb for that shrinkage. ETH.MESH.03917375. Actual shrinkage rates vary based on the individual patient, type of mesh, and location of mesh in the body.

(MSDS) which is intended to provide those handling or working with the product instructions and information on how to handle the substance in a safe matter. The MSDS for the TVT polypropylene states:

> Incompatibility
>
> The following materials are incompatible with this product: Strong oxidizers such as chlorine, peroxides, chromates, nitric acid, perchlorates, concentrated oxygen, sodium hypochlorite, calcium hypochlorite and permanganates. Chlorine; Nitric acid;[86]

While the plastic used to make the TVT mesh is also used in a number of other Ethicon products, including Prolene hernia mesh and Prolene sutures, this warning is particularly important as it applies to the TVT mesh, as the TVT mesh is intended to be placed in the vagina, which is a ready and natural source of peroxides, a strong oxidizer. Peroxides are regularly produced naturally by a woman's body. The Prolene hernia mesh is not intended to be placed in vagina, and the TVT mesh contains approximately 1,000 times more plastic material than a Prolene suture, so the clinical effects of oxidization would be markedly different between a suture and the TVT mesh.

This warning in the Prolene MSDS should have triggered an investigation into the effects that the naturally occurring oxidizers in the vaginal would have on the TVT mesh prior to Ethicon's marketing of the device, particularly with regard to oxidation and degradation of the mesh, as well as inflammation caused the presence of these naturally occurring substances in a woman's vagina. At the very least, Ethicon should have passed this warning along to surgeons and patients using the TVT mesh so they could make an informed choice about whether or not to use the device. However, no such warning regarding the TVT mesh's incompatibility with strong oxidizers has been communicated in the IFU, and Ethicon never did studies specifically

[86] Sunoco MSDS, 2003, 2005, 2009.

examining the clinical effect of these natural oxidizers on the TVT mesh. It is my opinion to a reasonable degree of medical certainty that Ethicon has failed in its duty as a reasonable medical device manufacturer by failing to include this warning in the IFU, and by failing to adequately study the clinical effects of the vagina's natural oxidizers on the TVT.

D. Ethicon Failed to Disclose and/or Downplayed Adverse Risks, Complications and Product Information in its Instructions for Use ("IFU") for the TVT

Ethicon's Instructions for Use ("IFU") fails to disclose important safety and risk information to physicians thereby compromising the ability for all levels of surgeons to adequately and appropriately consent their patients prior to the implantation of the TVT device. The IFU serves as the main modality for information regarding surgery. The IFU is the one document that Ethicon knew all surgeons see prior to the implantation of the TVT device.[87] In addition, according to Ethicon's Medical Director Piet Hinoul, physicians should be allowed to rely on the safety information in the IFU standing alone.[88] For this reason and according to Ethicon's own Regulatory and Medical Affairs, all risks associated with a medical device must be included in the products' IFU.[89] This is true so that all physicians know the safety and risk information known to a company and related to a specific product. In this case, the IFU for the TVT only lists the following information in its Adverse Risks Section for the TVT:

> Adverse Reactions
>
> * Punctures or lacerations of vessels, nerves, bladder or bowel may occur during needle passage and may require surgical repair.
>
> * Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation.

[87] Deposition of Dr. Richard Isenberg November 6, 2013 566:4-8
[88] Deposition of Dr. Piet Hinoul, January 14, 2014, 1207:18-1208:11
[89] Deposition of Catherine Beath, July 12, 2012, 592:7-11, Deposition of Dr. Marty Weisberg, August 9, 2013, 959:19-960:15

> * As with all foreign bodies, PROLENE mesh may potentiate an existing infection. The plastic sheath initially covering the PROLENE mesh is designed to minimize the risk of contamination.
>
> * Over correction, i.e., too much tension applied to the tape may cause temporary or permanent lower urinary tract obstruction.

The IFU for the TVT fails to disclose numerous adverse risks, safety information and warnings that are associated with the product, including, among others, the following: Death, pain, chronic pelvic pain, permanent dyspareunia, permanent sexual dysfunction, injury and pain to partner during sexual intercourse, negative impact on sexual function, vagina anatomic distortion, inability to remove the device, permanent risks for erosions, surgical interventions, development of worsening incontinence and urinary dysfunction. My review of internal documents and the depositions of Ethicon employees reveals that Ethicon was aware of these risks before or at the time the TVT was first marketed and sold.[90] In my opinion, Ethicon's failure to warn of these significant risks makes the TVT defective.

Additionally, Ethicon not only failed to disclose certain defects related to the product in the IFU, they downplayed several of the actual defects. The defects related to the mesh that Ethicon failed to disclose in its IFU are as follows: roping, curling, fraying, particle loss, degradation, contraction and shrinkage, chronic foreign body reaction and decreased pore size. In addition, Ethicon failed to disclose risks and information related to cytoxicity and the MSDS discussed above. Ethicon's decision to forgo adequate warnings of these defective characteristics of the TVT, also makes the TVT defective.

Ethicon also failed to include warnings in its IFU related to the increased risk of mesh extrusion in women with prior vaginal surgeries, vaginal atrophy, vaginal injury and post-

[90] Deposition of Piet Hinoul, June 27, 2013 552:2-9; Deposition of Catherine Beath, July 12, 2013; 608:13-20

operative infection.[91] In addition, Ethicon failed to inform physicians that the TVT procedure performed under general anesthesia increases the risk of urinary retention, erosions and failure of the surgery. All of the above risks safety and warning information was known to Ethicon prior to or around the time that the TVT was first marketed. Finally, Ethicon did not tell physicians that the TVT device would not work as well in smokers or obese patients.[92] Ethicon failed to act like a reasonable medical device manufacturer by failing to include the above risk, safety and warning information. The failure to include this information deprived physicians of the information and prevented them from truly and fully being able to consent their patients prior implanting TVT devices.

Ethicon also downplays and misrepresents significant information in its IFU related to certain mesh properties. Despite the significant amount of data regarding mesh-related inflammatory response, the original and the revised IFU for TVT claim that implantation of Gynecare TVT mesh "elicits a minimum to slight inflammatory reaction, which is transient". This is not true as the inflammatory response is chronic according to my clinical experience with the mesh and the testimony of Ethicon Medical Directors David Robinson and Piet Hinoul and is extensively documented in dozens of dozens of Ethicon documents.[93]

In addition, Ethicon states in its IFU that the mesh is not subject to degradation, which is also inconsistent with Ethicon internal studies and documents. In short, Ethicon not only failed to disclose certain risks associated with the product, it downplayed or inaccurately portrayed issues related to the mesh in the IFU. Thus, Ethicon failed to act like an appropriate medical device manufacturer in this regard. Ethicon prevented physicians from being able to have an

[91] Deposition of Rick Isenberg, November 6, 2013 582:17-583:1, ETH.MESH.00159634 at 00159697; ETH.MESH.00203456.
92 ETH.MESH.00640394, Deposition of Aaron Kirkemo, January 7, 2014, 556:4-19; 556:24-557:1; 557:5-558:21
93 Deposition of Dr. David Robinson, September 11, 2013, 1087:7-1089:15; Deposition of Dr. Piet Hinoul, January 14, 2014, 1192:4-1199:12; ETH.MESH.02340504 TVT IFU; ETH.MESH.00339437-442 "5 Years of Proven Performance" Feb 2002

appropriate and accurate informed consent discussion with their patients by concealing and misrepresenting this type of information. As a result, numerous patients have suffered injuries from the TVT device that were not disclosed to them as potential adverse risks related to the TVT.

Interestingly, in May 2015, Ethicon issued a new IFU which adds numerous new risks and warnings for the first time, including but not limited to acute and/or chronic pain, dyspareunia to patients and partners that may not resolve and that one or more revision surgeries maybe be necessary to treat adverse reactions. [94] As stated above, Ethicon had knowledge of these risks prior to the time the TVT was first marketed or sold.

E. Ethicon Failed To Conduct Appropriate Studies Related to the TVT

Ethicon has never conducted a long-term randomized controlled trial with safety as a primary endpoint.[95] There are also very few studies which have actually studied chronic, long-term pain with the TVT.[96] In addition, to my knowledge, with respect to studies performed by persons outside of Ethicon, very few are long term randomized controlled studies and none include a primary endpoint of safety.[97] There have also been recent studies that suggest that the studies assessing risks of synthetic mid-urethral slings to date are poor and that long term data or evidence lags behind shorter-term studies.[98]

Ethicon routinely relies and promotes its products based on long-term data that originates from the original Ulmsten (and later Nillson) data and studies. However, the studies lack significant data and fail to consider or inquire about many safety risks on the original patient

[94] TVT IFU, May, 2015
[95] Trial Testimony of Piet Hinoul in Linda Batiste Trial, 3-27-14 pm 57:9-12, 57:9-12
[96] Deposition of Dr. David Robinson, September 11, 2013, 978:7-14
[97] Deposition of David Robinson, 977:2-18
[98] Ford, et. al. Mid-urethral sling operations for stress urinary incontinence in women (review). The Cochrane Library, DOI: 10-1002/14651858.CD006375.pub3 (2015); Blaivas, et. al. Safety considerations for synthetic sling surgery. Nat. Rev. Urol. 18 August 2015, e-publication ahead of print.

cohort. The Ulmsten/Nillson data is also biased in that Dr. Ulmsten had financial incentives to obtain certain results with his original studies and received numerous payments, consulting agreements and royalties related to the TVT and his involvement with Ethicon.

F. Ethicon Failed to Consider Numerous Known Risks and Hazards of the TVT in its Design Process

As part of its design process, Ethicon is required to look at the potential risks of the implant. [99] According to Ethicon's Former Medical Director, there is a very formal process related to FMEAs, failure modes and risk analysis in determining different ways that things go wrong.[100] In making these determinations about risks, Ethicon relies on medical expertise from urologist like me to project what potential harms might result based on experience and literature. [101] According to Ethicon, a risk assessment is required to take into account all of the potential harms a product can cause once implanted.[102]

I have reviewed the relevant risk assessment documents created as part of the design of the mechanical-cut TVT, including the Preventia risk analysis performed by Medscand AB in 2000 and the updated Risk Assessment done in 2002.[103] These risk assessments leave out or do not take into account numerous risks and complications related to the TVT, including roping, curling, deforming, fraying, particle loss, degradation, contraction and shrinkage, chronic foreign body reaction and decreased pore size due to its heavyweight and/or the fact that the device is impossible or difficult to remove. Based on testimony and internal documents I have reviewed and discussed above, Ethicon had knowledge of these risks at the time the TVT was launched.[104] As a result, Ethicon should have taken these into account during the design of the TVT and

[99] Deposition of Dr. Aaron Kirkemo, January 6, 2014, 36:15-38:16
[100] Deposition of Dr. Aaron Kirkemo, January 6, 2014, 36:15-38:16
[101] Deposition of Dr. Aaron Kirkemo, January 6, 2014, 36:15-38:16
[102] Deposition of Scott Ciarocca, March 29, 2012, 97:23-98:21
[103] ETH.MESH.01317508
[104] Deposition of Piet Hinoul, June 27, 2013 552:2-9; Deposition of Catherine Beath, July 12, 2013; 608:13-20

should have designed out these defects or warned about them. Because Ethicon failed to do so, the risks of the TVT are too great, and outweigh the benefits of the product.

For the reasons set forth above, Ethicon fell below the standard of care of a reasonable and prudent medical device manufacturer by using the old construction mesh in the TVT device as it should not be used in the pelvic floor when implanted in this manner. These design defects of the mesh and the TVT lead to long term complications, pain, acute and chronic pelvic pain, vaginal pain, permanent dyspareunia, injury and pain to partner during sexual intercourse, negative impact on sexual function, the possibility of multiple pelvic erosions that can occur throughout one's lifetime, vaginal scarring, vagina anatomic distortion, inability to remove the device, permanent risks for erosions, need for multiple surgical interventions, development of worsening incontinence and urinary dysfunction including urinary urgency, urinary urge incontinence, urinary retention, suprapubic pain, suprapubic numbness, pain with lifting, pain with ambulation, and pain with sitting.

V. Exhibits

My current curriculum vitae is attached as Exhibit A.

All materials that have been available to me to consider in support of my finding and opinions are included above and listed below in Exhibit B.

VI. Recent Testimony

I have testified as an expert at the following trial:

Coloplast A/S v. Generical Medical Devices; United States District Court – Western District of Washington at Tacoma Case No. C10-227BHS

Linda Gross et al. v. Gynecare, et al.; Superior Court of New Jersey Law Division – Middlesex County Case No. MID-L-9131-08

Diane Bellew v. Ethicon et al.; United States District Court, Southern District of West Virginia Case No. 2:12-cv-22473

Janice L. St. Cyr v. C.R. Bard, Inc. et al.; United States District Court, Southern District of West Virginia Case No. 2:14-cv-02313

Kathleen Stanbrough v. C.R. Bard, Inc. et al.; United States District Court, Southern District of West Virginia Case No. 2:14-cv-06937

Sheila Sutton v. C.R. Bard, Inc. et al.; United States District Court, Southern District of West Virginia Case No. 2:14-cv-00105

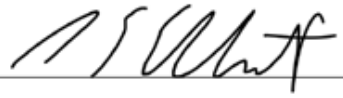
Pamela Ailey v Cook Medical, Inc., et al.; United States District Court, Southern District of West Virginia Case No. 2:13-CV-20496

VII. Compensation

I am compensated for investigation, study and consultation in the case at the rate of $700.00 per hour.

February 1, 2016

DATE



DANIEL ELLIOTT, M.D.